

PATENT SPECIFICATION

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(54) 1-SUBSTITUTED-3-AMIDOPYRROLIDINES

(71) We, A. H. ROBINS COMPANY, INCORPORATED, a Corporation organised and existing under the Laws of the State of Virginia, United States of America, of 1407 Cummings Drive, Richmond, Virginia 23220, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly 5 described in and by the following statement:—

The present invention relates to certain novel 1-substituted-3-amidopyrrolidines, to a process for the preparation of such compounds, 15 to pharmaceutical compositions containing them, to processes for making them and to their use.

The compounds of the present invention have the formula:



Formula I.

wherein;

R represents hydrogen, lower alkyl, allyl, phenyl, phenoxy-lower alkyl, cyclohexyl or phenyl-lower alkyl;

25 R¹ represents hydrogen, lower alkyl, phenyl, cyclohexyl, lower-alkoxy phenyl, hydroxy-phenyl, halophenyl or trifluoromethylphenyl; and

30 R² represents lower alkyl, phenyl, nitro-phenyl, aminophenyl, halophenyl, lower-alkoxy phenyl, phenoxy-lower alkyl, halo-phenoxy-lower-alkyl, lower-alkyl-phenyl or trifluoromethylphenyl; with the proviso that when R is lower alkyl, R¹ cannot be hydrogen.

35 The invention also embraces acid addition salts of such compounds.

In this specification the following terms have the meanings indicated.

The term "lower alkyl" means straight or branched chain radicals of up to eight carbon atoms inclusive, preferably of no more than six carbon atoms, and is exemplified by such groups as methyl, ethyl, propyl, isopropyl, butyl, sec. butyl, tertiary butyl, amyl, isoamyl, hexyl, heptyl and octyl.

A "lower alkoxy" group has the formula —O—lower alkyl.

The term "lower alkenyl" means straight and branched chain radicals of two up to eight carbon atoms inclusive and is exemplified by such groups as vinyl, allyl, methallyl, 4-pentenyl, 3-hexenyl and 3-methyl-3-heptenyl.

The term "lower cycloalkyl" means cyclic radicals containing three up to nine carbon atoms inclusive and encompasses such groups as cyclopropyl, cyclobutyl, cyclohexyl, cyclopentyl, methylcyclohexyl, propylcyclohexyl, ethylcyclopentyl, propylcyclopentyl, dimethylcyclohexyl, cycloheptyl and cyclooctyl.

The term "phenyl-lower-alkyl" as used herein includes such groups as benzyl, phenethyl and phenpropyl.

By the term "phenyl" is meant the unsubstituted phenyl radical and phenyl radicals substituted by one or more substituents which are not reactive or otherwise interfering under the conditions of reaction in the processes for making the compounds. Such substituents include lower alkyl, lower alkoxy, trifluoromethyl, nitro, hydroxy, chloro, bromo and fluoro. The substituted phenyl radicals have preferably no more than three such substituents which can be in various available positions of the phenyl nucleus, and when more than one substituent is present, these can be the same or different and can be in various position combinations relative to each other. The lower alkyl and lower alkoxy substituents each have preferably

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from one to four carbon atoms which can be arranged as straight or branched chains. A total of nine carbon atoms in all ring substituents, making a total of fifteen carbon atoms in the radical, is the preferred maximum.

5 "Phenoxy" has the formula —O—phenyl. The compounds of the invention are useful because of their pharmacological action on the 10 central nervous system as analgetics, anti-depressants or both. The activity is demonstrable when the compounds are used in the form of their free base or in the form of their non-toxic acid addition salts. The preferred form 15 of the compounds is as their non-toxic acid addition salts for increased water solubility and ease of administration.

The analgetic effect of some compounds 20 of this invention was evaluated by the procedure of P. Nilsen, *Acta Pharmacol. et Toxicol.* 18, 10 (1961). The dose effective in 50 per cent of the treated mice is recorded in the following table as compared with the compounds known as "Darvon" and 25 "Demerol". The actual compounds tested were those described hereinafter in the respective Examples.

		ED ₅₀ mg/kg.
30	Compound of Example:	
	3	5.7
	4	6.8
	5	8.0
35	14	2.0
	15	5.2
	17	14.2
	18	3.4
	31	16.5
40	"Darvon"	11.2
	"Demerol"*	6.4

*Demerol is a trade mark

The anti-depressant effect of some compounds of this invention was assessed by their ability to antagonize the depressant actions of 45 tetrabenazine (2 - oxo - 3 - isobutyl - 9,10 - dimethoxy - 1,2,3,4,6,7 - hexahydro - 11bH-benzo[a]quinolizine) in mice [Englehardt et al. *J. Med. Chem.* 11 (2), 325 (1968)]. The dose effective in 50 per cent of the treated mice is 50 recorded in the following table as compared with the compounds known as "Tofranil" and "Elavil".

Compound of Example:	ED ₅₀ mg/kg.	
15	0.6	55
29	1.7	
36	2.8	
37	2.8	
38	4.8	60
39	9.0	
40	15.5	
41	4.9	
42	2.4	
44	2.0	65
47	4.9	
48	0.6	
"Tofranil"*	1.3	
"Elavil"	1.1	

*TOFRANIL is a trade mark

As already indicated, the invention includes acid addition salts of the bases of Formula I with organic and inorganic acids. Such salts are easily prepared by methods known in the art. When the compounds are to be used as intermediates for preparing other compounds or for any non-pharmaceutical use, the toxicity or non-toxicity of the salt is immaterial. When the compounds are to be used as pharmaceuticals, they are most conveniently used in the form of non-toxic acid addition salts. Both toxic and non-toxic salts are therefore within the scope of the invention. The acids which can be used to prepare the non-toxic acid addition salts are those which produce, when combined with the free base, salts whose anions are relatively innocuous in therapeutic doses of the salts, so that beneficial physiological properties inherent in the free bases are not vitiated by side effects ascribable to the anions.

The base may be reacted with the calculated amount of organic or inorganic acid in a solvent miscible with water, such as ethanol or isopropanol, with isolation of the salt by concentration and cooling, or the base may be reacted with an excess of the acid in a solvent immiscible with water, such as ethyl ether or isopropyl ether, with the desired salt separating directly. Exemplary of such organic salts are those formed with citric, acetic, lactic, maleic, fumaric, benzoic, tartaric, ascorbic, pamoic, succinic, methanesulphonic, malic, citraconic and itaconic acids. Exemplary of such inorganic salts are those formed with

hydrochloric, hydrobromic, sulphuric, phosphoric and nitric acids.

In general, the novel compounds of this invention may be prepared by acylating appropriate 1-substituted-3-amino-pyrrolidine starting materials with the corresponding acid chloride or an acid anhydride to give the corresponding amides embraced by Formula I.

The 1-substituted-3-aminopyrrolidine starting materials may be prepared according to methods disclosed in United States Patent Specification No. 3,337,580. Generally, a 1-substituted-3-pyrrolidinol is converted to a 1-substituted-3-halo-, a 3-alkylsulphonyloxy- or a 3-aryl-sulphonyloxy-pyrrolidine which is reacted with a primary aromatic amine, for example aniline or a substituted aniline, or with a non-aromatic primary amine such as cyclohexylamine, cyclopentyl amine, methylamine or ethylamine, to give 1-substituted-3-amino-pyrrolidines.

In an alternative method, a 1-substituted-3-halopyrrolidine, a 1-substituted-3-alkylsulphonyloxy-pyrrolidine or a 1-substituted-3-aryl-sulphonyloxy-pyrrolidine is reacted with phthalimide in the form of its alkali metal salt according to methods described in United States Patent Specification No. 3,316,276 to give N-(1-substituted-3-pyrrolidinyl) phthalimides which are reduced with hydrazine hydrate to 1-substituted-3-aminopyrrolidines.

A suitable general procedure for preparing the 1-substituted-3-amidopyrrolidines of this invention, using the starting materials given above is as follows:—

A solution of an acid chloride in a suitable organic solvent, for example chloroform, is added dropwise to a stirred heterogeneous chloroform-water solution containing a 1-substituted-3-aminopyrrolidine and a suitable acid acceptor which can be a metal carbonate or a water-soluble lower alkylamine. The mixture is stirred for a period of from about 30 minutes to about one hour at room temperature. The organic layer is separated from the aqueous layer, dried over an inert drying agent, for example sodium sulphate, and evaporated *in vacuo*. The residual crude 1-substituted-3-amidopyrrolidine is purified by distillation *in vacuo* and converted to an acid addition salt which is further purified by recrystallization, chromatography on magnesium silicate, or crystallization from a suitable solvent.

In an alternative method, the 1-substituted-3-amino-pyrrolidine is dissolved in a solvent,

110 Analysis: Calculated for $C_{17}H_{11}N_3O_3$:
Found:

for example chloroform, benzene or toluene, and an acid chloride or an acid anhydride dissolved in the same solvent is added and the reaction mixture is refluxed gently for a period of from about 6 hours to about 16 hours. The solvent is evaporated from the reaction mixture and the residue is treated with a base such as dilute sodium hydroxide solution or sodium bicarbonate solution and the product is isolated by extraction from the aqueous base with an organic solvent, for example, benzene or ether, and evaporation of the solvent. The product may be purified by methods described above.

The 1-benzyl-3-amidopyrrolidines are catalytically hydrogenolysed, for example in the Paar hydrogenator in about three atmospheres of hydrogen and at about 50°C, using palladium on charcoal catalyst, to the corresponding 3-amidopyrrolidines of formula I in which R represents a hydrogen atom, which are isolated and purified by methods described above. Compounds containing a nitro-substituent on a phenyl ring are catalytically reduced in the same manner, generally at room temperature, to the corresponding amine.

The 3-amidopyrrolidines may be further reacted with lower-alkyl halides, phenyl lower-alkyl halides or phenoxy lower-alkyl halides to give additional 1-substituted-3-amidopyrrolidines within the scope of Formula I. The reaction may be carried out in an organic solvent such as chloroform, benzene or toluene containing an inorganic acid binder such as a metal carbonate. The reaction mixture is stirred, usually at the reflux temperature of the solvent employed, cooled, washed with water, concentrated and the residual material remaining after evaporation of the organic solvent is purified by one of the methods described above.

EXAMPLE 1

1-Phenyl-3-(4-nitrobenzamido)pyrrolidine.

A solution of 6.9 g (0.037 mole) of 4-nitrobenzoyl chloride in 30 ml of chloroform was added dropwise at room temperature to a stirred mixture of 6 g (0.037 mole) of 1-phenyl-3-aminopyrrolidine and 10 g of potassium carbonate in 30 ml of water and 30 ml of chloroform. The mixture was stirred for 30 minutes, the chloroform layer separated, dried over magnesium sulphate and evaporated. Recrystallization of the crude solid residue from alcohol-water gave 10.6 g (92%) of an orange solid which melted at 153—155°C.

C, 65.58; H, 5.50; N, 13.50
C, 65.40; H, 5.42; N, 13.41

was shaken in a Paar hydrogenator in three atmospheres of hydrogen at room temperature. The reduction mixture was filtered and the filtrate concentrated to give 3.8 g of crystalline product which melted at 213—216°C.

115 Analysis: Calculated for $C_{17}H_{11}N_3O$:
Found:

C, 72.57; H, 6.81; N, 14.94
C, 72.74; H, 6.76; N, 15.09

EXAMPLE 3

1-Benzyl-3-(N-phenylpropionamido)-
pyrrolidine.

5 A stirred mixture of 25.2 g (0.1 mole) of 1-benzyl-3-anilinopyrrolidine and 30 g of potassium carbonate in 200 ml of chloroform was treated dropwise with 10 g (0.11 mole) of propionyl chloride in 25 ml of chloroform.

Analysis: Calculated for $C_{20}H_{23}N_2O$: C, 77.88; H, 7.84; N, 9.08
Found: C, 77.75; H, 7.86; N, 8.92

EXAMPLE 4

20 1-(2-Phenoxyethyl)-3-[N-(2-methoxyphenyl)-
propionamido]pyrrolidine.

25 A mixture of 5 g (0.02 mole) of 3-[N-(2-methoxyphenyl)propionamido]pyrrolidine, 4.05 g (0.02 mole) of 2-phenoxyethyl bromide 5 g of sodium bicarbonate and 50 ml of isopropanol was refluxed for eight hours. The mixture was diluted with water, extracted with

Analysis: Calculated for $C_{22}H_{25}N_2O_3$: C, 71.71; H, 7.66; N, 7.60
Found: C, 71.84; H, 7.71; N, 7.58

EXAMPLES 5-13

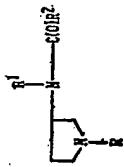
40 The physical constants for Examples 5 to 13 are tabulated in Table I. The compounds were

After addition, the mixture was stirred for four hours, 100 ml of water added, the mixture stirred for 30 minutes, the chloroform layer separated, dried over magnesium sulphate and evaporated under reduced pressure to an oil. The pure product distilled at 180°C/0.02 mm to give 24 g (78%) of product. The oil solidified on standing and melted at 57-60°C. 10
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chloroform, the chloroform extracts combined, dried over magnesium sulphate and evaporated to an oil (8 g). The oil was dissolved in benzene and chromatographed on 250 g of 60-100 mesh magnesium silicate. The column was eluted with benzene containing increasing amounts of acetone. The pure product, 3.8 g (52%), was molecularly distilled 30
35 for analysis.

prepared according to the procedures described in Examples 1 to 3.

TABLE I



Example	R ₁	R ₂	C ₆ H ₅	C ₂ H ₅	139—41	62.05 61.76	6.94 6.86	Analysis		
								C Calcd. Found	H Calcd. Found	N Calcd. Found
5 ¹	CH ₃ CH=CH ₂	C ₆ H ₅	C ₆ H ₅	C ₂ H ₅	139—41	62.05 61.76	6.94 6.86	8.04 8.08		
6	C ₆ H ₅	CH ₃	C ₆ H ₄ —4NO ₂	C ₆ H ₄ —4NH ₂	149—50	66.44 66.37	5.89 5.93	12.92 12.83		
7	C ₆ H ₅	CH ₃	C ₆ H ₄ —4NH ₂	C ₆ H ₄ —4NH ₂	168—70	73.19 72.77	7.17 7.10	14.23 14.22		
8	C ₆ H ₅	H	C ₂ H ₅	C ₂ H ₅	135—37	71.52 71.29	8.31 8.13	12.83 12.88		
9	C ₆ H ₅	H	C ₆ H ₅	C ₆ H ₅	153—55	76.66 76.58	6.81 6.72	10.52 10.48		
10	C ₆ H ₅	n-C ₄ H ₉	C ₆ H ₄ —4NH ₂	C ₆ H ₄ —4NH ₂	—	74.74 74.66	8.07 7.91	12.45 12.49		
11	C ₆ H ₅ —CH ₂ —	2-CH ₃ OC ₆ H ₄	C ₂ H ₅	C ₂ H ₅	190/0.03 mm.	74.52 74.34	7.74 7.74	8.28 8.40		
12 ²	H	2-CH ₃ OC ₆ H ₄	C ₂ H ₅	C ₂ H ₅	132—35	59.33 59.26	6.64 6.63	7.69 7.72		
13	C ₆ H ₅	C ₆ H ₅	CH ₃ OC ₆ H ₄ —4Cl	CH ₃ OC ₆ H ₄ —4Cl	—	66.93 66.60	6.46 6.60	7.81 7.70		

¹ oxalate salt² fumarate salt

EXAMPLE 14
 1-Phenethyl-3-(N-phenylpropionamido)-
 pyrrolidine Fumarate.

A mixture of 1-phenethyl-3-anilino-
 5 pyrrolidine (10.0 g; 0.038 mole), propionic
 anhydride (5.9 g; 0.045 mole) and 50 ml of
 benzene was refluxed for four hours, cooled
 and washed with 10% sodium bicarbonate and
 water. The benzene solution was dried over
 sodium sulphate and the solvent was evaporated. The residual oil (11 g), fumaric acid (2.7
 g; 0.023 mole) and 100 ml of isopropanol were
 refluxed for 15 minutes, filtered, cooled and
 the filtrate diluted with isopropyl ether. The
 crystalline product melted at 105—107.5°C
 after several recrystallizations from iso-
 propanol-isopropyl ether and weighed 6.9 g
 (59% yield). 10

Analysis: Calculated for $C_{25}H_{30}N_2O_5$:
 20 Found: C, 68.47; H, 6.90; N, 6.39
 C, 68.30; H, 6.90; N, 6.47

EXAMPLE 15
 1-Methyl-3-[N-phenyl-(4-chlorobenzamido)]-
 pyrrolidine Fumarate.

A solution of 4-chlorobenzoyl chloride prepared from 10.9 g (0.07 mole) of 4-chlorobenzoic acid and excess thionyl chloride in 50 ml of chloroform was added slowly to 10.6 g (0.06 mole) of 1-methyl-3-anilinopyrrolidine in 40 ml of chloroform. The mixture was refluxed at 25 gently for 16 hours, the solvent evaporated at 30 reduced pressure, the residue treated with 100 ml of 2N sodium hydroxide solution and the basic mixture extracted with two 200 ml portions of ether. The combined ether extracts were washed several times with cold water, dried over magnesium sulphate, and concentrated to yield a residue which weighed 18.2 g (97% yield). The fumarate salt which was prepared using isopropanol-isopropyl ether 35 melted at 124—126°C. 40

Analysis: Calculated for $C_{22}H_{23}ClN_2O_5$:
 Found: C, 61.32; H, 5.38; N, 6.50
 C, 60.95; H, 5.55; N, 6.74

EXAMPLE 16
 1-Ethyl-3-[N-(3-trifluoromethylphenyl)-
 45 propionamido]pyrrolidine Fumarate.

A mixture of 20.0 g (0.078 mole) of 1-ethyl-
 3-(3-trifluoromethylanilino)pyrrolidine, 13.7 g
 (0.095 mole) of propionic anhydride, several
 50 drops of pyridine and 100 ml of benzene was
 refluxed for 16 hours. The cooled mixture was
 washed with 10% sodium bicarbonate solu-
 tion and water. The benzene was evaporated,
 the residual oil was distilled at reduced pres-
 sure and the fraction boiling at 103—105°C/
 0.05 mm collected. The colourless, non-viscous
 55 oil weighed 15.0 g (61% yield). The fumarate
 salt which was prepared using isopropanol-isop-
 propyl ether weighed 10.5 g (85% yield) and
 melted at 155—156°C. 55

60 Analysis: Calculated for $C_{20}H_{25}N_2O_5F_3$:
 Found: C, 55.81; H, 5.85; N, 6.51
 C, 55.86; H, 5.98; N, 6.47

EXAMPLE 17
 1-(2-Phenoxyethyl)-3-(N-phenylpropion-
 amido)pyrrolidine Hydrochloride.

A mixture of 9.9 g (0.035 mole) of 3-
 65 anilino-1-(2-phenoxyethyl)pyrrolidine, 6.5 g
 (0.05 mole) of propionic anhydride and 50 ml
 of benzene was refluxed for 16 hours, cooled
 and washed with 10% sodium bicarbonate
 solution and water. The solvent was evapo-
 rated and the residual oil was distilled at re-
 duced pressure. The colourless, viscous oil dis-
 tillied at 183—185°C/0.03 mm and weighed
 70 8.5 g (72% yield). The hydrochloride salt
 which was prepared was recrystallized several
 times from an isopropanol-isopropyl ether mix-
 ture and melted at 115—118°C. 75

Analysis: Calculated for $C_{21}H_{27}ClN_2O_5$:
 Found: C, 67.27; H, 7.26; N, 7.47
 C, 67.33; H, 7.28; N, 7.36

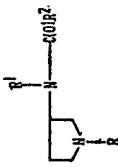
80 **EXAMPLE 18**
 1-[2-(2-Methoxyphenoxy)ethyl]-3-(N-
 phenylpropionamido)pyrrolidine.

A mixture of 7.8 g (0.025 mole) of 3-
 85 anilino-1-[2-(2-methoxyphenoxy)ethyl]-
 pyrrolidine, 5.9 g (0.045 mole) of propionic
 anhydride and 50 ml of benzene was refluxed
 for 16 hours, cooled and washed with 10%
 sodium bicarbonate and water. The benzene
 solution was dried over magnesium sulphate,
 the solvent evaporated, and the residual oil
 in benzene was chromatographed on 300 g of
 90 60—100 mesh magnesium silicate, eluting with
 a 1% methanol-benzene mixture. The product
 weighed 4.5 g (49% yield). A portion of the
 oil was distilled at reduced pressure and the
 fraction distilling at 192—194°C/0.002 mm
 collected. 95

Analysis: Calculated for $C_{22}H_{28}N_2O_5$:
 Found: C, 71.71; H, 7.66; N, 7.60
 C, 71.57; H, 7.60; N, 7.47

100 **EXAMPLES 19—48**
 The physical constants for Examples 19 to
 48 are tabulated in Table II. The compounds
 were prepared according to the procedures de-
 scribed in Examples 14 to 18.

TABLE II



Example	R	R ¹	R ²	R ³	Analysis			
					M.P. B.P./mm. °C	C Calcd. Found	H Calcd. Found	N Calcd. Found
19 ^a	CH ₃	C ₆ H ₅	CH ₃	CH ₃	110—13	61.06 59.69	6.63 6.37	8.38 8.28
20	C ₆ H ₅ CH ₂ —	H	CH ₃		165/0.05 mm.	71.52 71.42	8.31 8.35	12.84 12.71
21 ¹	CH ₃	C ₆ H ₅	C ₆ H ₅		133—34	62.05 62.10	6.94 6.97	8.04 8.08
22 ^a	C ₆ H ₅ CH ₂	C ₆ H ₄ —2OH	C ₆ H ₅		92—94	63.76 63.45	6.32 6.40	6.76 6.57
23	C ₆ H ₅ CH ₂ —	C ₆ H ₄ —3OH	C ₆ H ₅		122.5—24.5	74.04 74.16	7.46 7.43	8.63 8.59
24 ¹	CH ₃	C ₆ H ₁₁	C ₆ H ₂ —3,4,5CH ₃ O	169—71.5	60.96 60.60	7.32 7.40	5.68 5.77	
25	C ₆ H ₁₁	H	C ₆ H ₄ —4NO ₂		152—53	64.33 64.23	7.30 7.34	13.24 13.27
26	CH ₃	C ₆ H ₅	C ₆ H ₅ CH ₃	135—140/0.04 mm.	77.52 76.88	7.53 7.54	9.52 9.36	

TABLE II (Continued)

Example	R	R ¹	R ²	C ₆ H ₄ —4NH ₂	M.P. B.P./mm. °C.	Analysis		
						C Calcd. Found	H Calcd. Found	N Calcd. Found
27 ^a	C ₆ H ₁₁	H			98—100	66.85 66.51	8.91 8.74	13.76 13.73
28	C ₆ H ₅ CH ₂ —	H		C ₆ H ₂ —3,4,5CH ₃ O	128—29	68.09 68.00	7.08 7.26	7.56 7.62
29	CH ₃	C ₆ H ₅		C ₆ H ₆	97—99	77.11 77.08	7.19 7.24	9.99 9.96
30 ^a	CH ₃	C ₆ H ₅		C ₆ H ₂ —3,4,5CH ₃ O	154—55	61.72 62.03	6.22 6.08	5.76 5.79
31 ^a	CH ₃	C ₆ H ₅		CH ₂ OC ₆ H ₄ —4Cl	105—108	59.93 60.12	5.47 5.64	6.08 6.17
32	C ₆ H ₅	H		CH ₂ OC ₆ H ₄ —4Cl	99—101	65.50 65.30	5.79 5.91	8.48 8.47
33 ^a	C ₂ H ₆	C ₄ H ₉		CH ₂ OC ₆ H ₄ —4Cl	142—44	—	—	7.47 7.28
34 ^a	CH ₃	C ₆ H ₅		CH ₂ OC ₆ H ₅	138—39	62.99 62.97	6.04 6.01	7.00 7.03
35	C ₆ H ₁₁	H		—C ₆ H ₅	129—130	74.96 75.20	8.88 8.83	10.29 10.28
36 ^a	CH ₃	C ₆ H ₅		C ₆ H ₄ —3CF ₃	92—95	57.53 57.66	4.83 5.01	6.39 6.33
37 ^a	CH ₃	C ₆ H ₅		C ₆ H ₄ —3Cl	124.5—126.5	59.33 59.28	5.23 5.26	6.92 6.97
38 ^a	CH ₃	C ₆ H ₅		C ₆ H ₄ —4F	127—129	61.85 61.65	5.45 5.55	7.21 7.22

TABLE II (Continued)

Example	R	R ¹	R ²	M.P. B.P./num. °C.	Analysis		
					C Calcd. Found	H Calcd. Found	N Calcd. Found
39 ^a	C ₆ H ₅ C ₂ H ₄	C ₆ H ₅	C ₆ H ₄ —4Cl	152—154	65.52 65.27	5.50 5.55	5.66 5.60
40	CH ₃	C ₆ H ₅	C ₆ H ₄ —4Br	75—80	60.18 60.22	5.33 5.22	7.80 7.73
41 ^b	C ₆ H ₅ CH ₃	C ₆ H ₅	C ₆ H ₅	192—193	73.36 73.11	6.41 6.47	7.13 7.02
42 ^c	H	C ₆ H ₅	C ₆ H ₅	187—189	67.43 67.18	6.32 6.39	9.25 9.14
43 ^c	CH ₃	C ₆ H ₅	C ₆ H ₄ —4CH ₃ O	139.5—141.5	62.99 62.95	6.04 6.07	7.00 6.92
44 ^a	C ₂ H ₅	C ₆ H ₄ —3CF ₃	C ₆ H ₅	110—112	58.40 58.40	5.12 5.22	6.19 6.18
45 ^c	C ₂ H ₅	C ₆ H ₄ —4Cl	C ₆ H ₅	164.5—167	62.46 62.62	6.07 6.09	7.69 7.61
46 ^c	CH ₃	C ₆ H ₅	C ₆ H ₄ —4CH ₃	158—160	65.61 65.68	6.29 6.32	7.29 7.31
47 ^c	C ₂ H ₅	C ₆ H ₄ —4Cl	C ₆ H ₄ —4Cl	207—209	57.08 57.39	5.30 5.28	7.01 7.01
48 ^c	C ₂ H ₅	C ₆ H ₅	C ₆ H ₄ —4Cl	131—132	60.21 59.97	5.53 5.53	6.69 6.63

¹ fumarate salt, ² oxalate salt, ³ hydrate, ⁴ maleate salt, ⁵ hydrochloride salt.

Formulation and Administration

Useful compositions containing at least one of the compounds according to the invention in association with a pharmaceutical carrier or excipient may be prepared in accordance with conventional technology and procedures. Thus, the compounds may be presented in a form suitable for oral or parenteral administration. For example, compositions for oral administration can be solid or liquid and can take the form of capsules, tablets, coated tablets and suspensions, such compositions comprising carriers or excipients conveniently used in the pharmaceutical art. Suitable tabletting excipients include lactose, potato and maize starches, talc, gelatin, stearic and silicic acids, magnesium stearate and polyvinyl pyrrolidone. For parenteral administration, the carrier or excipient may be a sterile, parenterally acceptable liquid; e.g. water or a parenterally acceptable oil, such as arachis oil, contained in ampoules.

Advantageously, the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredients. Tablets, capsules, coated tablets and ampoules are examples of preferred dosage unit forms. Each dosage unit adapted for oral administration can conveniently contain 5 to 500 mg and preferably 20 to 200 mg of the active ingredient, whereas each dosage unit adapted for intramuscular administration can conveniently contain 5 to 100 mg and preferably 10 to 75 mg of the active ingredient.

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The following formulations are representative for all of the pharmacologically active compounds of the invention, and especially a pharmacologically acceptable salt thereof.

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1. *Capsules* — Capsules of 5, 25, and 50 mg of active ingredient per capsule are prepared. With the higher amounts of active ingredient, reduction may be made in the amount of lactose.

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2. *Tablets* — A typical formulation for a tablet containing 5 mg of active ingredient per tablet follows. The formulation may be used for other strengths of active ingredient by adjustment of weight of dicalcium phosphate.

40

Typical blend for encapsulation		Per capsule, mg.
45	Active ingredient, as salt	5.0
	Lactose	296.7
	Starch	129.0
	Magnesium stearate	4.3
	Total	435.0

50 2. *Tablets* — A typical formulation for a tablet containing 5 mg of active ingredient per tablet follows. The formulation may be used for other strengths of active ingredient by adjustment of weight of dicalcium phosphate.

contain a higher dosage of the active ingredient and are as follows:

Per tablet, mg.	
1. Active ingredient, as salt	5.0
2. Corn starch	13.6
3. Corn starch (paste)	3.4
4. Lactose	79.2
5. Dicalcium phosphate	68.2
6. Calcium stearate	0.9
Total	170.3 mg.

65 60 Uniformly blend 1, 2, 4 and 5. Prepare 3 as a ten per cent paste in water. Granulate the blend with starch paste and pass the wet mass through an eight-mesh screen. The wet granulation is dried and sized through a twelve-mesh screen. The dried granules are blended with the calcium stearate and compressed.

70 Additional tablet formulations preferably

50 mg Tablet. Ingredients	Per tablet, mg.	75
Active ingredient, as salt	50.0	
Lactose	90.0	
"Milo" starch*	20.0	
Corn starch	38.0	
Calcium stearate	2.0	80
Total	200.0 mg.	

*MILO is a trade mark

85 Uniformly blend the active ingredient, lactose, starches, and dicalcium phosphate when present. The blend is then granulated using water as a granulating medium. The wet granules are passed through an eight-mesh screen and dried at 140-160° F overnight. The dried granules are passed through a ten-mesh screen, blended with the calcium stearate, and the lubricated granules then converted into tablets on a suitable tablet press.

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3. Injectable—2% sterile solution		Per cc	
Active ingredient		20 mg.	
Preservative, e.g., chlorbutanol	0.5%	weight/volume	
Water for injection		q.s.	
5 Prepare solution, clarify by filtration, fill into vials, seal, and autoclave.			
WHAT WE CLAIM IS:—			
1. Compounds having the formula:			
10 wherein;			
	R represents hydrogen, lower-alkyl, allyl, phenyl, phenoxy-lower-alkyl, cyclohexyl or phenyl-lower-alkyl;		
15	R ¹ represents hydrogen, lower-alkyl, phenyl, cyclohexyl, lower-alkoxy phenyl, hydroxy-phenyl, halophenyl or trifluoromethylphenyl; and		
	R ² represents lower-alkyl, phenyl, nitro-phenyl, aminophenyl, halophenyl, lower-alkoxy-phenyl, phenoxy-lower-alkyl, halo-phenoxy-lower-alkyl, lower-alkyl-phenyl or trifluoromethylphenyl;		
20	with the proviso that when R is lower alkyl, R ¹ cannot be hydrogen.		
25	2. 1 - Benzyl - 3 - (N - phenylpropion-amido)pyrrolidine.		
	3. 1 - (2 - Phenoxyethyl) - 3 - [N - (2 - methoxyphenyl)propionamido]pyrrolidine.		
30	4. 1 - Allyl - 3 - (N - phenylpropionamido)pyrrolidine.		
	5. 1 - (2 - Phenylethyl) - 3 - (N - phenyl-propionamido)pyrrolidine.		
	6. 1 - Methyl - 3 - (N - phenyl - 4 - chlorobenzamido)pyrrolidine.		
35	7. 1 - (2 - Phenoxyethyl) - 3 - (N - phenyl-propionamido)pyrrolidine.		
	8. 1 - [2 - (o - Methoxy - phenoxy)ethyl] - 3-(N-phenylpropionamido)pyrrolidine.		
40	9. 1 - Methyl - 3 - (N - phenylbenzamido)pyrrolidine.		
	10. 1 - Ethyl - 3 - (N - phenyl - 4 - chlorobenzamido)pyrrolidine.		
	11. 1 - Ethyl - 3 - [N - (3 - trifluoromethyl-phenyl)benzamido]pyrrolidine.		
45	12. 1 - Methyl - 3 - (N - phenyl - 3 - trifluoromethylbenzamido)pyrrolidine.		
	13. 1 - Methyl - 3 - (N - phenyl - 3 - chlorobenzamido)pyrrolidine.		
	14. 1 - Methyl - 3 - (N - phenyl - 4 - fluorobenzamido)pyrrolidine.		
50	15. 3-(N-Phenylbenzamido)-pyrrolidine.		
	16. A process for the preparation of com-		
			pounds as claimed in Claim 1 which comprises acylating the appropriate 1-substituted-3-aminopyrrolidine with the corresponding acid chloride or acid anhydride. 55
			17. A process as claimed in Claim 16 in which the product is a 1-benzyl-3-amido-pyrrolidine which is then catalytically hydrogenated to give a compound as claimed in Claim 1 in which R represents a hydrogen atom. 60
			18. A process as claimed in Claim 17 which comprises reacting the resulting 3-amido-pyrrolidine with a lower-alkyl halide, phenyl lower-alkyl halide, or phenoxy lower-alkyl halide. 65
			19. 1 - Substituted - 3 - amidopyrrolidines which have been prepared by a process as claimed in any of Claims 16 to 18. 70
			20. Acid addition salts of compounds as claimed in any of Claims 1 to 15 or 19. 75
			21. A process for preparing 1-substituted-3-amidopyrrolidines, substantially as described in any of the Examples. 80
			22. 1 - Substituted - 3 - amidopyrrolidines which have been prepared by a process as claimed in Claim 21. 85
			23. Pharmaceutical compositions useful for analgetic effects, comprising a compound or non-toxic acid addition salt as claimed in any of Claims 1 to 15, 19, 20 or 22 and a pharmaceutically acceptable carrier or excipient. 90
			24. Pharmaceutical compositions as claimed in Claim 23 in unit dosage form containing, for oral administration from 5 to 500 milligrams or for intramuscular administration from 5 to 100 milligrams, of the said compound or salt per unit. 95
			25. A method which comprises administering to a living animal body (other than man) an analgetically effective amount of a compound or salt as claimed in any of Claims 1 to 15, 19, 20 or 22. 95
			26. A method as claimed in Claim 25 wherein the compound is administered together with a pharmaceutically acceptable carrier or excipient therefor and in an amount of 5 to 500 milligrams. 95
			KILBURN & STRODE, Chartered Patent Agents, Agents for the Applicants.
			Reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949, to Patent No. 1,088,531.

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